Epidemiol. Infect. (2016), **144**, 2363–2370. © Cambridge University Press 2016
doi:10.1017/S0950268816000625

Characteristics and consequences of medical care interruptions in HIV-infected patients in France

L. CUZIN[1]*, P. DELLAMONICA[2], Y. YAZDANPANAH[3], S. BOUCHEZ[4], D. REY[5], B. HOEN[6] AND A. CABIÉ[7] for the Dat'AIDS Study Group†

[1] *INSERM, UMR 1027, Toulouse, France; Université de Toulouse III, Toulouse, France; CHU Toulouse, COREVIH Midi Pyrénées Limousin, France*
[2] *Infectious Diseases Unit, Nice University Hospital, France*
[3] *Infectious and Tropical Diseases Unit, Bichat Hospital, Paris, ATIP-AVENIR Inserm U1137, Paris Diderot University, Paris, France*
[4] *Infectious Diseases Unit, Nantes University Hospital, France*
[5] *HIV/AIDS Center, Strasbourg University Hospital, France*
[6] *Infectious Diseases Unit, Pointe à Pitre University Hospital, French West Indies*
[7] *Infectious Diseases Unit, Fort de France University Hospital, French West Indies*

Received 7 April 2015; Final revision 10 February 2016; Accepted 7 March 2016; first published online 1 April 2016

SUMMARY

To describe the consequences of medical care interruptions (MCIs) we selected patients with at least two medical encounters between January 2006 and June 2013 in the Dat'AIDS cohort. Patients with any time interval >15 months between two visits were defined as having a MCI, as opposed to uninterrupted follow-up (UFU). Patients' characteristics at the time of HIV diagnosis and at the censoring date were compared between groups. Cox proportional hazards models were built to assess the role of interruptions on survival (total and AIDS-free). Of 11 116 patients, 824 had at least one MCI. These patients were younger at the time of HIV diagnosis (30 *vs.* 33 years, $P < 0{\cdot}0001$). MCI was less frequent in men having sex with men *vs.* heterosexual patients [odds ratio (OR) 0·81, 95% confidence interval (CI) 0·69–0·96)], and a centre effect was described. MCI was independently associated with AIDS (OR 2·54, 95% CI 2·10–3·09) and death (OR 2·65, 95% CI 1·94–3·61). At the censoring date, 52·2% of patients with at least one MCI had viral load below detection *vs.* 85·3% of the UFU group ($P < 0{\cdot}0001$). In conclusion, MCIs were associated with patients' survival and with the proportion of viral loads below detection in our cohort, compromising individual and collective treatment benefits.

Key words: AIDS-free survival, care retention, HIV, lost to follow-up, virological control.

INTRODUCTION

On an individual level, linkage and retention to care are known to be critical for HIV-infected patients [1]. At the population level, this will allow a decrease in the community viral load (VL) and consequently a decrease in HIV transmission [2–4]. The Centers for Disease Control and Prevention estimated that the proportion of virologically suppressed individuals in HIV-diagnosed patients in the USA was 35% [5], mainly due to issues such as access to care, or adherence to care and treatment. Access to care is highly dependent on the healthcare system, and very different estimations have been made in countries with large

* Author for correspondence: Miss L. Cuzin, COREVIH, Batiment Turiaf, Hopital Purpan, TSA40031, 31059 Toulouse cedex, France. (Email: cuzin.l@chu-toulouse.fr)
† Members of the Dat'AIDS Study Group are given in the Appendix.

and free access to care and treatment in Europe and in France [6, 7].

One of the key steps on the road from infection to durable virological suppression is adherence to care. Incidence rate of lost-to-follow-up (LTFU) has been estimated in Europe to be around 4/100 person-years, with significant differences between the European regions [8]. Age, absence of prescribed anti-retroviral therapy (ART), detectable VL while receiving therapy, intravenous drug use, CD4 cell counts, and time since HIV diagnosis have been shown to be associated with higher risks of LTFU in various studies [8–10].

Due to the unavoidable fatal outcome of HIV infection in the absence of treatment, those patients are due to return to care at some time after care interruption. The consequences of medical care interruptions (MCIs) have not been studied in recent years. In a recent study people known to be HIV-positive but not seeking care for their infection accounted for as much as 53% of new opportunistic infections [11]. At the public health level, where it is desirable to have as many HIV-infected patients as possible with a VL below detection, MCIs are challenging if they result in more patients having a detectable VL even after they resume care.

The objective of this study was to describe the characteristics of patients who had had at least one MCI during their follow-up, and the individual and collective consequences of these interruptions.

METHODS

Information was collected from seven HIV reference centres in France that maintain prospective databases of all HIV-infected patients who sought care and provided written consent [12]. The databases collect demographic, clinical, antiretroviral history, VL, and CD4 cell count data at regular 3- to 6-month intervals during routine clinical assessment. Patients who changed facility during their follow-up are counted only once, i.e. in the last facility they attended. For the purpose of this study, we selected all patients with at least two clinical assessments registered in the database between 1 January 2006 and 30 June 2013. All data were censored on 30 June 2013.

Patients who had at least one time interval of >15 months between two visits were defined to have at least one MCI, as opposed to the remaining patients who had uninterrupted follow-up (UFU). The time gap of 15 months was chosen because French recommendations imply a hospital visit at least once a year, with possible intermediate clinical visits to a general physician [13]. We considered that patients presenting with a VL below detection level at the return-to-care visit could have been receiving care elsewhere during the considered interruption, they were therefore not considered in the study. MCI patients with missing data regarding CD4 or VL at the time of care interruption or at the time of care resumption were excluded. They were compared to patients with at least one MCI in order to identify a possible bias due to their exclusion.

Patients' characteristics at their inclusion in the database: age at HIV diagnosis, sex, most probable route of infection, hepatitis B or C co-infection, year of HIV diagnosis and the centre providing care were compared between the two groups.

At the end of the study period proportions of patients receiving ART, CDC classification, proportions of patients with VL below detection, vital status, cause of death, CD4 cell counts, AIDS-free and overall survival were also compared between the two groups.

Of patients with at least one MCI, duration of MCI, year of interruption, duration of known infection at the time of MCI, CD4 and VL values before and after MCI, prescribed ART before and after MCI, and new AIDS-defining events were described. As having a VL below detection (50 copies/ml) can be considered an indicator of efficient care, the characteristics were also described in patients with a VL below detection at the time of care interruption and in those without.

Categorical data were described by percentages and compared by χ^2 method, continuous data were described by medians and interquartile range (IQR), and their distributions were compared between groups using Kruskal–Wallis non-parametrical tests. All individual characteristics associated with care interruption ($P < 0{\cdot}1$) were included in a multivariable logistic regression model in order to estimate independent associations. Mean times from HIV diagnosis to a first AIDS-defining event and to death were estimated by Kaplan–Meier methods. Cox proportional hazards models were built to assess the potential effect of care interruptions on the occurrence of AIDS or death in addition to baseline characteristics as fixed covariables. As a MCI may occur before or after the first AIDS-defining event, MCIs were treated as time-dependent variables in the model built to assess the potential effect of care interruptions on occurrence

https://doi.org/10.1017/S0950268816000625 Published online by Cambridge University Press

of AIDS [14]. MCI(t) took the value 0 in the case of UFU and in case of MCI if the MCI occurred after the first AIDS-defining event; and the value 1 if MCI occurred before the first AIDS-defining event. In the Cox model built to assess the potential effect of care interruptions on death, MCI took the value 0 before the occurrence of a MCI and 1 afterwards. All statistics were performed using SAS v. 9.4 (SAS Institute Inc., USA).

RESULTS

Of the 16 205 patients included in the cohort, 12 014 had had at least two clinical visits during the study period. Of these, 10 292 patients were classified as having UFU, and 1722 had at least one time interval between two clinical visits >15 months. Of those, 721 were not taken into consideration because of VL below detection at the first back-to-care visit. Of the patients with at least one MCI, 177 were excluded because of missing values either for CD4 cell counts or VL at the time of interruption or at the back-to-care visit. Thus the population of patients with at least one MCI included 824 patients, be compared to the 10 292 with UFU (Fig. 1). Comparisons between excluded patients and patients with at least one MCI regarding sex, age at HIV diagnosis, presence of viral hepatitis co-infection, most probable route of infection, and vital status at the end of the study did not show any difference.

Comparisons between UFU and MCI patients and the regression results appear in Table 1. The MCI patients were significantly younger than UFU patients at the time of HIV diagnosis (median 30 *vs.* 33 years, $P < 0{\cdot}0001$), with a lower risk of MCI with increasing age. The most probable route of infection was associated with MCI, men who have sex with men having a lower risk [odds ratio (OR) 0·81, 95% confidence interval (CI) 0·69–0·96] compared to heterosexual patients. Some differences also appeared between the centres in which individuals sought care, one centre having a significant independent association with MCI (OR 1·54, 95% CI 1·10–2·10). Median length of known infection was not different between groups.

At the end of the study period, compared to UFU patients, patients with at least one MCI were receiving ART less frequently (91·5% *vs.* 97%, respectively, $P < 0{\cdot}0001$), were more frequently classified as AIDS cases (32% *vs.* 24·3, respectively, $P < 0{\cdot}0001$), and a greater proportion of patients had detectable VL (47·8% *vs.* 14·7%, respectively, $P < 0{\cdot}0001$). All the comparisons are shown in Table 2.

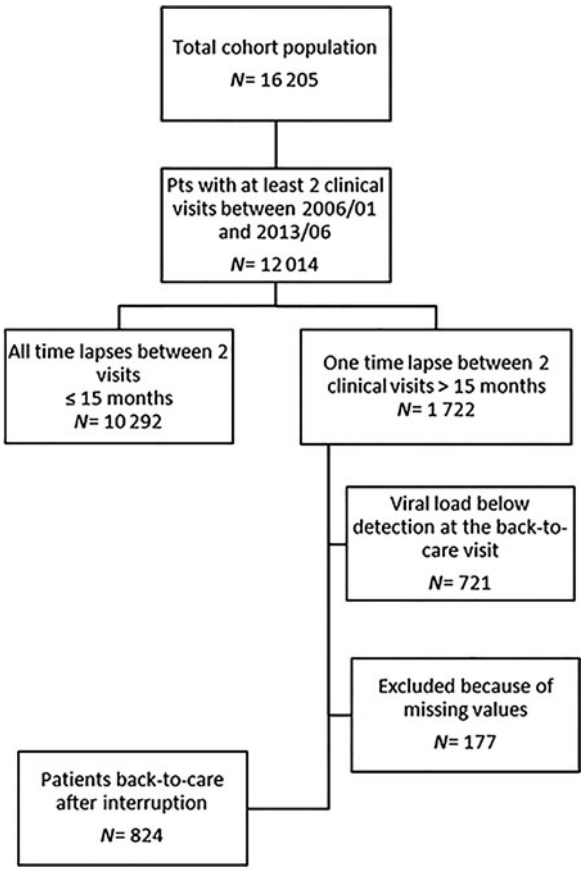

Fig. 1. Selection of patients from the cohort.

A first AIDS-defining event was reported in 91 patients after care resumption. In 53 cases this event was the very reason to return to care (date of event <1 month after the back-to-care visit). Those 53 cases included mostly avoidable opportunistic infections: pneumocystis pneumonia (12 cases), cerebral toxoplasmosis (seven cases), profound candidiasis (six cases), cryptococcosis (six cases), progressive multifocal leukoencephalopathy (five cases), AIDS dementia (four cases), tuberculosis (three cases), lymphomas (two cases), cytomegalovirus infection (one case), Kaposi's sarcoma (two cases), and multiple infections (four cases). The 38 other first AIDS-defining events occurred later: median time 10 months (IQR 7–26). They included: pneumocystis pneumonia (seven cases), profound candidiasis (six cases), tuberculosis (five cases), Kaposi sarcoma (five cases), lymphomas (four cases), cytomegalovirus infection (three cases), cerebral toxoplasmosis (three cases), AIDS dementia (two cases), multiple infections (two cases) and progressive multifocal leukoencephalopathy (one case).

https://doi.org/10.1017/S0950268816000625 Published online by Cambridge University Press

Table 1. *Patients' characteristics at inclusion in the cohort, univariate and multivariate risk ratios for medical care interruption*

					Univariate		Multivariate	
	Total ($N = 11\,116$)	UFU ($N = 10\,292$)	MCI ($N = 824$)	*P*	RR	95% CI	RR	95% CI
Age at HIV diagnosis, years, median (IQR)	33 (26–41)	33 (26–42)	30 (25–38)	<0·001				
<27					Ref.	–	Ref.	–
27–34					0·78	0·66–0·94	0·72	0·59–0·86
35–40					0·60	0·48–0·73	0·49	0·39–0·61
>40					0·47	0·39–0·58	0·39	0·31–0·48
Sex, *n* (%)								
Women	3363 (30·2)	3118 (30·3)	245 (29·7)	0·7	Ref.	–		
Men	7753 (69·3)	7174 (69·7)	579 (70·3)		1·02	0·88–1·20		
Most probable route of infection, *n* (%)								
Heterosexual	5088 (45·8)	4691 (45·6)	397 (48·2)	0·0004	Ref.	–	Ref	–
Homosexual/bisexual	4271 (38·4)	4000 (38·9)	271 (32·9)		0·80	0·68–0·94	0·87	0·74–1·35
Materno-fetal	90 (0·8)	84 (0·8)	6 (0·7)		0·84	0·36–0·94	0·72	0·31–1·69
Blood products/IVDU	1176 (10·6)	1058 (10·3)	118 (14·3)		1·32	1·06–1·64	1·41	1·07–1·87
Other/unknown	487 (4·4)	455 (4·4)	32 (3·9)		0·83	0·57–1·31	0·94	0·64–1·38
Duration of known HIV infection , years, median (IQR)	13 (6–20)	13 (6–20)	12 (7–9)	0·97				
Year of HIV diagnosis, *n* (%)								
<1993	2814 (25·3)	2645 (25·7)	169 (20·5)	<0·0001	Ref.		Ref.	–
1993–1999	2602 (23·4)	2384 (23·1)	218 (26·5)		1·43	1·16–1·76	2·02	1·61–2·55
2000–2006	3050 (27·4)	2742 (26·7)	308 (37·4)		1·76	1·45–2·14	2·80	2·23–3·52
>2006	2650 (23·9)	2521 (24·5)	129 (15·6)		0·8	0·63–1·01	1·32	1·01–1·72
Hepatitis co-infection, *n* (%)								
No	8877 (79·8)	8254 (80·2)	623 (75·6)	0·002	Ref.	–	Ref	–
Yes	2239 (20·2)	2038 (19·8)	201 (24·4)		1·31	1·11–1·54	1·21	0·98–1·49
HIV care centre, *n* (%)								
A	1004 (9)	932 (9)	72 (8·7)	0·002	Ref.	–	Ref.	–
B	986 (8·9)	911 (8·9)	75 (9·1)		1·07	0·76–1·49	1·16	0·82–1·65
C	914 (8·2)	822 (8)	92 (11·2)		1·45	1·05–2·00	1·60	1·15–2·33
D	2365 (21·3)	2209 (21·5)	156 (18·9)		0·91	0·68–1·22	0·98	0·73–1·32
E	2009 (18·1)	1839 (17·9)	170 (20·6)		1·19	0·89–1·59	1·20	0·90–1·61
F	1639 (14·7)	1542 (15)	97 (11·8)		0·81	0·59–1·12	0·83	0·61–1·15
G	2199 (19·8)	2037 (19·7)	162 (19·7)		1·03	0·77–1·37	1·07	0·79–1·45

IQR, Interquartile range; UFU, uninterrupted followed-up patients; MCI, patients with at least one medical care interruption; RR, risk ratio; CI, confidence interval; IVDU, intravenous drug user.

Table 2. *Patients' characteristics at the end of the study period*

	Total, *N* (%) [11 116 (100)]	UFU, *N* (%) [10 292 (92·6)]	MCI, *N* (%) [824 (7·4)]	*P*
Receiving ART, *n* (%)				
Yes	10 713 (96)	9959 (97)	754 (91·5)	<0·0001
No	403 (4)	333 (3)	70 (8·5)	
CDC stage C, *n* (%)				
Yes	2766 (24·9)	2502 (24·3)	264 (32)	<0·0001
No	8350 (75·1)	7790 (75·7)	560 (68)	
Last VL below detection, *n* (%)				
Yes	9197 (82·9)	8777 (85·3)	420 (52·2)	<0·0001
No	1900 (17·1)	1515 (14·7)	385 (47·8)	
Vital status, *n* (%)				
Alive	10 609 (95·4)	9829 (95·5)	780 (94·7)	0·26
Dead	507 (4·6)	463 (4·5)	44 (5·3)	
Cause of death, *n* (%)				
AIDS related	101 (20)	82 (17·7)	19 (43)	0·0007
Other	406 (80)	381 (82·3)	25 (57)	
Died with VL below detection, *n* (%)				
Yes	320 (63)	305 (66)	15 (34)	<0·0001
No	187 (37)	158 (34)	29 (66)	
Last CD4 cell count value, median (IQR)	591 (416–783)	601 (433–793)	397 (221–625)	0·0001

UFU, Uninterrupted followed-up patients; MCI, patients with at least one medical care interruption; ART, anti-retroviral therapy; VL, viral load; IQR, interquartile range.

Table 3. *Characteristics associated with risk of AIDS and death, Cox proportional hazards model with care interruptions as time dependent*

	AIDS free survival*		Overall survival†	
	HR	95% CI	HR	95% CI
Medical care interruption	2·54	2·10–3·09	2·65	1·94–3·61
Most probable route of infection				
Heterosexual	Ref.	–	Ref.	–
Homosexual/bisexual	0·89	0·81–0·97	0·738	0·59–0·92
Materno-fetal	0·76	0·50–1·17	0·38	0·13–1·27
Blood products/IVDU	0·86	0·75–0·99	1·03	0·81–1·31
Other/unknown	1·39	1·16–1·67	1·44	0·90–2·30
HIV care centre				
A	Ref.	–	Ref.	–
B	2·51	2·09–3·03	1·59	0·99–2·56
C	1·84	1·51–2·23	2·28	1·44–3·44
D	1·38	1·16–1·63	1·05	0·70–1·56
E	1·63	1·37–1·94	1·57	1·04–2·37
F	1·29	1·08–1·55	1·57	1·04–2·36
G	1·27	1·07–1·51	0·99	0·66–1·47
Hepatitis co-infection	1·21	1·09–1·35	1·35	1·06–1·71

HR, Hazard ratio; CI, confidence interval; IVDU, intravenous drug user.
* From time of HIV diagnosis to the first AIDS defining event or date of censoring;
† From time of HIV diagnosis to the date of death or date of censoring.

https://doi.org/10.1017/S0950268816000625 Published online by Cambridge University Press

Table 4. *Medical care interruptions: description and consequences*

	N (%)	VL below detection at LVBI *N* (%)	Detectable VL at LVBI *N* (%)	*P*
Year of LVBI				
2006	174 (21)	33 (19)	141 (81)	0·004
2007	172 (21)	31 (18)	141 (82)	
2008	142 (17)	29 (20)	113 (80)	
2009	142 (17)	36 (25)	106 (75)	
2010	124 (15)	34 (27)	90 (73)	
2011 and first quarter of 2012	70 (9)	28 (54)	42 (46)	
ART prescription at LVBI, by year of interruption (Y/N; % treated)*		Among the patients receiving ART		
2006	107/67 (61·6)	32 (29·9)	75 (70·1)	0·07
2007	92/80 (53·5)	29 (31·5)	63 (68·5)	
2008	99/43 (69·7)	28 (28·3)	71 (71·7)	
2009	102/40 (71·8)	36 (35·3)	66 (64·7)	
2010	90/34 (72·6)	34 (37·8)	56 (62·2)	
2011 and first quarter of 2012	54/16 (77·1)	28 (51·8)	26 (48·2)	
First AIDS defining event after care resumption	91 (11)	18	73	
Duration of known HIV infection at LBVI (months), median (IQR)	93·5 (30·5 to 171)	138 (67 to 215)	76 (24 to 163)	<0·001
Duration of interruption (months), median (IQR)	22 (18 to 32)	22 (17 to 31)	23 (18 to 32)	0·20
CD4 cell count at LBVI (/mm^3), median (IQR)	434 (274 to 605)	445 (294 to 632)	428 (268 to 597)	0·10
CD4 cell count at the time of care resumption (/mm^3), median (IQR)	287 (135 to 478)	245 (107 to 464)	298 (143 to 488)	0·28
Loss in CD4 cells during interruption (/mm^3), median (IQR)	−114 (−242 to −8)	−161 (−334 to −6)	−107 (−224 to −8)	0·01

VL, Viral load; LVBI, last visit before interruption; ART, anti-retroviral therapy.
* $P < 0·001$.

The mean times from HIV diagnosis to the first AIDS-defining event were 18 and 21 years, respectively for patients with at least one MCI and with UFU, respectively ($P = 0·0003$). The mean times from HIV diagnosis to death were 25 and 29 years, respectively for MCI and UFU patients ($P = 0·09$). Of patients with at least one MCI, death was HIV-related in 43% of cases, compared to 17·7% of deaths in patients with UFU ($P = 0·0007$). Table 3 shows the results of the proportional Cox hazards models. MCI patients had significantly higher risk of death and AIDS [hazard ratio (HR) 2·64 (95% CI 1·94–3·61) and HR 2·55 (95% CI 2·10–3·09), respectively]. Most probable route of infection and HIV care centre were also associated with AIDS-free and overall survival.

The median duration of MCI was 22 months (IQR 18–32). The description of the interruptions and their consequences are shown in Table 4. With passing years, more patients were receiving ART at the time of last visit before interruption (from 61·6% in 2006 to 77·1% in 2011, $P < 0·001$), meanwhile the proportion of treated patients with detectable VL at the time of interruption decreased from 70% in 2006 to 48% in 2011 ($P = 0·07$).

DISCUSSION

In this large multi-centre cohort we found that MCIs had a deleterious effect for patients, with significant loss in CD4 cell count and increased risk of death and AIDS.

The characteristics of patients with MCI were similar to those previously described in LTFU patients: young age, and absence of ART prescription at the time of interruption [8–10]. Hopefully, the widening of the recommendations to treat each and every patient will allow some decrease in care interruptions. However, prescribing ART is just one step in the care continuum, and efforts are still needed to address the multiplicity of barriers faced by individuals across each step [15]. It is wearisome that in our study, despite greater frequency of ART prescription over the passing years, most of the patients still had detectable VL at the time of MCI.

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We have shown that the proportion of patients with at least one MCI compared to patients with UFU is different between centres. It is important to know that some of the centres have proactive methods for bringing patients back-to-care in case of LTFU [9, 16], so it was predictable that they would have greater proportions of back-to-care patients. Those methods can be as simple and cost-effective as phone calls, text messages or e-mails, and should be implemented in all the centres to reduce the proportion of patients with MCIs.

Of the 91 patients who presented with a first AIDS-defining event after care resumption, more than a half returned to care for that very reason. It is noteworthy that most of these events could have been avoided with efficient follow-up. Even if the designs are quite different, they can be compared with the results of the study published by Lee *et al.* who found that half of acute opportunistic infections were described in patients who were informed of their HIV infection but not seeking care [11].

The impact of MCIs on AIDS-free and overall survival is clear in the multivariate Cox model, even if the Kaplan–Meier estimation failed to show a significant difference between groups regarding overall survival, probably because of the small proportion of deaths. This impact had already been shown in a smaller French cohort in patients in care between 1997 and 2006 [1]. AIDS-related mortality has been decreasing in France from 47% of all HIV-infected patients' deaths in 2000 to 25% in 2010, but the authors underline that this is still high in a country with universal access to care [17]. Without doubt, MCIs play a role in this persistent proportion of AIDS-related deaths.

At the public health level MCIs also have consequences, as at the end of the study period patients with past MCI frequently had less VLs below detection thresholds. It has been published recently that patients who are less likely to stay in care are those who are more likely to be at risk of transmitting HIV to others because more often they do not receive ART and have high VLs [16]. Unfortunately, our results show that these differences are persistent even after care resumption.

The strength of our study lies with the population size, the multicentre design and the long study period; however, this study also has limits. First, the patients we considered to have follow-up interrupted could have been seeking care elsewhere during the considered care interruption. To minimize this potential classification bias, we did not consider interruptions when the first VL obtained after care resumption was below the detectable threshold. Second, due to the retrospective design of the study, we could not assess the reasons why patients interrupted their follow-up at a given time, nor the reason why they came back (apart from the 53 AIDS-defining events concomitant with the back-to-care visit), although this information might be of great importance in designing strategies to limit the phenomenon.

In conclusion, we found that even in the most recent years and in a country with universal access to care and treatment, MCIs remained associated with individual damage. They also represent a threat to the global aim of HIV-incidence reduction by universal treatment access.

APPENDIX. Dat'AIDS Study Group

P. Enel, V. Obry-Roguet, O. Faucher, S. Bregigeon, I. Poizot-Martin, (Marseille); B. Marchou, P. Massip, E. Bonnet, M. Obadia, M. Alvarez, L. Porte, L. Cuzin, P. Delobel, M. Chauveau, D. Garipuy, I. Lepain, M. Marcel, E. Puntis, K. Sauné (Toulouse); P. Pugliese, C. Ceppi, E. Cua, J. Cottalorda, P. Dellamonica, E. Demonchy, B. Dunais, J. Durant, C. Etienne, S. Ferrando, J. G. Fuzibet, R. Garraffo, K. Risso, V. Mondain, A. Naqvi, N. Oran, I. Perbost, S. Pillet, B. Prouvost-Keller, C. Pradier, S. Wehrlen-Pugliese, E. Rosenthal, S. Sausse, P.M. Roger (Nice); C. Allavena, C. Bernaud, E. Billaud, C. Biron, B. Bonnet, S. Bouchez, D. Boutoille, C. Brunet-Cartier, N. Hall, T. Jovelin, P. Morineau, F. Raffi, V. Reliquet, H. Hue, L. Larmet, So. Pineau (Nantes); A. Cheret, P. Choisy (Tourcoing); Y. Yazdanpanah, C. Duvivier, M.A. Valantin, R. Agher, C. Katlama, Michka Shoai-Tehrani, O. Lortholary, P.H. Consigny, G. Cessot, F. Touam, K. Benhadj (Paris); A. Cabié, S. Abel, S. Pierre-François (Fort de France) ; D. Rey, E. Ebel, P. Fischer, M. Partisani (Strasbourg); C. Chirouze, C. Drobacheff-Thiébaut, J.P. Faller, J.F. Faucher, A. Foltzer, H. Gil, L. Hustache-Mathieu, C. Bourdeaux (Besançon), B. Hoen (Pointe à Pitre)

ACKNOWLEDGEMENTS

This work did not require any funding.

DECLARATION OF INTEREST

None.

https://doi.org/10.1017/S0950268816000625 Published online by Cambridge University Press

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